UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/508,957	02/03/2005	Jonathan S. Stamler	STAM3002 PCT	6780

23364 7590 12/12/2007

BACON & THOMAS, PLLC
625 SLATERS LANE
FOURTH FLOOR
ALEXANDRIA, VA 22314

EXAMINER	
HUANG, GIGI GEORGIANA	
ART UNIT	**PAPER NUMBER**
1618	

MAIL DATE	DELIVERY MODE
12/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,957	STAMLER ET AL.	
	Examiner	Art Unit	
	GiGi Huang	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-41 and 69-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-41 and 69-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The amendment filed September 21, 2007 has been received, entered and carefully considered. The amendment affects the instant application accordingly:

(A) Claims 35, 37, and 40 have been amended.

(B) Claims 1-34 and 42-68 have been cancelled.

(C) Claims 69-74 have been added.

2. Claims 35-41 and 69-74 are pending in the case.

3. Claims 35-41 and 69-74 are present for examination.

4. The text of those sections of title 35.U.S. Code not included in this action can be found in the prior Office action.

Response to Arguments

5. Claims 35-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Applicant's arguments see pages 8-9 filed 09/21/2007 have been fully considered and are persuasive for claims 39 and 41. Applicant's arguments against the issue of treating a patient in need of nitroglycerin therapy are persuasive and withdrawn. Applicant arguments that the rejection did not apply to claims 39 and 41 are persuasive and withdrawn.

However, Applicant's arguments see pages 8-9 filed 09/21/2007 have been fully considered but they are not persuasive for claims 35-38 and 40. Applicant's arguments

against that the examiner did not meet the burden to show that one skilled in the art would not determine what a mitochondrial selective thiol would be- is not persuasive.

First, the claims are to a mitochondria selective dithiol and a "reductant capable of activating mtALDH" and not a mitochondria selective thiol, as the specification describes and delineates the distinction. Secondly, the MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated that, "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated that, "A written description of an invention

involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for a *prima facie* case has been discussed in the previous action.

The MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claims 35-38 and 40 are broad and generic, with respect to all possible compounds encompassed by the claims. The possible structural variations are limitless to any compound capable of reduction. Although the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the examples in the specification. Moreover, the specification lacks sufficient variety of species to reflect this variance in the genus. While having written description of two dithiols and one reductant: dithiothreitol (DTT), dihydrolipoic acid (DHLA) and tris (2-carboxyethylphosphine), and are identified in the specification

tables and/or examples, the specification does not provide sufficient descriptive support for the myriad of compounds embraced by the claims.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the entire scope of the claimed invention.

Whereby establishing the prima facie case, the burden is now shifted to the Applicant to show that they were in possession at the time of filing, the genus of compounds and that the genus is adequately described for one of skill in the art to identify. It is noted that Murphy addresses the concept that cellular thiols are critical in nitroglycerin therapy, but there is disagreement about their identity and the nature of any intermediates, which would thereby go to the issue of written description of the genus.

The rejection of claims 35-38 and 40 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained.

6. Claims 35-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of angina, an unstable coronary

syndrome, it does not reasonably provide enablement for *every* coronary syndrome and condition, restenosis, asthma, or rectal spasm.

Applicant's arguments see pages 9-11 filed 09/21/2007 have been fully considered but they are not persuasive. Applicant's arguments on the word "every" and routine application of Wands factors without evidence, and the statement that nitroglycerin does not work is not persuasive.

Applicant's issue of the word "every" is taken out of context as the scope of enablement is directed to the broad claim of coronary syndromes, restenosis, asthma, or rectal spasm. The claims as written need not show examples for every coronary syndrome but does need to show that they are enabled with a sufficient number of representative examples to be enabled for the generic term. The Applicant has reasonably demonstrated that the specific dithiols: dithiothreitol (DTT), dihydrolipoic acid (DHLA) and the reductant tris (2-carboxyethylphosphine) are useful as a therapeutic agent for delaying, postponing, and/or reducing nitroglycerin tolerance in angina. However, the Applicant does not show sufficient enablement for the broad genus of coronary syndromes. Applicant's statement that routine application of Wands factors without evidence had been applied is not persuasive as evidence has been provided that nitroglycerin use is contraindicated in coronary syndromes such as constrictive pericarditis and pericardial tamponade (see Physician Desk Reference pages).

As addressed in the previous action, Kennedy et al. (Airway response to sublingual nitroglycerin in acute asthma, JAMA), teaches the concept that nitroglycerin was inadequate for the treatment of acute asthma and did not significantly change

neither the forced expiratory volume nor the forced vital capacity of air for those tested showing that nitroglycerines in not adequate initial therapy for asthmatic attacks, in fact he teaches that its use could be dangerous.

The statement that nitroglycerin does not work is not persuasive as it is routinely utilized for angina for decades (PDR pages and Murphy-Introduction, first paragraph). The issue of the term "reverse" with respect to nitroglycerin tolerance is still applicable, as tolerance will still occur as there are two pathways and the compounds do lose effectiveness (see Murphy) over time, and the point of the conversion of mtALDH is not commensurate in scope with the claims as written. As addressed in the previous action, a terms such as "prevent" and "reverse" have a higher standard for enablement than does "therapeutic" or "treat", especially since it is notoriously well accepted in the medical art that the vast majority of afflictions/disorders suffered by mankind cannot be totally prevented or completely reversed with current therapies.

Applicant's statement that "a response that does not cite countering case law will be considered by the undersigned to be frivolous" is not persuasive as Applicant's references to case law does not express the specific details that would be relevant to the details of the instant claims, and the MPEP does not require the Examiner to state case law in response to arguments, as long as a prima facie case is established with a reasonable examination of the merits with evidence and support.

7. Claims 35-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There are no arguments, the rejection is maintained.

8. Claims 35-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Weischer et al. (DE 4420 102 A1).

Applicant's arguments see page 6 filed 09/21/2007 have been fully considered but they are not persuasive. Applicant's arguments are centered on the Weischer's treatment as synergistic, a substitute for increased dosage for nitroglycerin, no suggestion that tolerance can be reversed or postponed, and that alpha-lipoic acid is not administered after nitroglycerin. The arguments are not persuasive as the same steps are disclosed in Weischer and when the same components (nitroglycerin and alpha-lipoic acid) are administered to an individual, the same cascade and effect will inherently be produced. There does not need to be a suggestion that tolerance can be reversed or postponed as the effect will inherently occur. The argument of synergy and increase dosage is not persuasive as increased dosages of nitroglycerin as a result of tolerance so when the same components (nitroglycerin and alpha-lipoic acid) are administered and the same effects inherently occur, there is no need to increase dosages and the components are working together to the same results as claimed. It is noted that Weischer teaches the concept of the combination for tolerance on Page 2, paragraph 5 of the machine translation. The argument of the alpha-lipoic acid is not administered after nitroglycerin is no a claim limitation and not persuasive. It is noted that the patient population in need of nitroglycerin therapy would be the same patient population in need of reversal or postponement of nitroglycerin tolerance and the art still applies.

The rejection of claims 35-39 under 35 U.S.C. 102(b) as being anticipated by Weischer et al. (DE 4420 102 A1) is maintained.

9. Claims 35-38 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy (Influence of redox compounds on nitrovasodilator-induced relaxations of rat coronary arteries, British Journal of Pharmacology) in view of Laursen et al. (In Vivo Nitrate Tolerance Is Not Associated With Reduced Bioconversion of Nitroglycerin to Nitric Oxide, Circulation).

Applicant's arguments see pages 6-7, filed 09/21/2007 have been fully considered but they are not persuasive. Applicant's arguments are centered on Murphy not suggesting or teaching that tolerance can be reversed or postponed, no suggestion that DTT would reverse or postpone tolerance, or that nitroglycerin is administered before DTT. The arguments are not persuasive as the same steps are disclosed in Murphy and when in view of Laursen, would have been administered to a patient, and when the same components (nitroglycerin and DTT) are administered to an individual, the same cascade and effect will inherently be produced. There does not need to be a suggestion that tolerance can be reversed or postponed as the effect will inherently occur.

It is noted that the patient population in need of nitroglycerin therapy would be the same patient population in need of reversal or postponement of nitroglycerin tolerance and the art still applies.

The rejection of claims 35-38 and 40 under 35 U.S.C. 103(a) as being unpatentable over Murphy (Influence of redox compounds on nitrovasodilator-induced

relaxations of rat coronary arteries, British Journal of Pharmacology) in view of Laursen et al. (In Vivo Nitrate Tolerance Is Not Associated With Reduced Bioconversion of Nitroglycerin to Nitric Oxide, Circulation) is maintained.

10. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy in view of Laursen et al. as applied to claims 35-38 and 40 above, and in view of Prugin et al. (Interplay between Vitamin E, Glutathione and Dihydrolipoic Acid in Protection against Lipid Peroxidation, Abstract only).

Applicant's arguments see page 7, filed 09/21/2007 have been fully considered but they are not persuasive. Applicant's arguments are centered on the arguments for Murphy and Laursen et al., the response to the arguments is addressed above.

The rejection of claim 39 under 35 U.S.C. 103(a) as being unpatentable over Murphy in view of Laursen et al. as applied to claims 35-38 and 40 above, and in view of Prugin et al. (Interplay between Vitamin E, Glutathione and Dihydrolipoic Acid in Protection against Lipid Peroxidation, Abstract only) is maintained.

11. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy in view of Laursen et al. as applied to claims 35-38 and 40 above, and in view of Getz et al. (A Comparison between the Sulfhydryl Reductants Tris(2-carboxyethyl)phosphine and Dithiothreitol for Use in Protein Biochemistry, Analytical Biochemistry).

Applicant's arguments see page 7, filed 09/21/2007 have been fully considered but they are not persuasive. Applicant's arguments are centered on the arguments for Murphy and Laursen et al., the response to the arguments is addressed above.

The rejection of claim 41 under 35 U.S.C. 103(a) as being unpatentable over Murphy in view of Laursen et al. as applied to claims 35-38 and 40 above, and in view of Getz et al. (A Comparison between the Sulfhydryl Reductants Tris(2-carboxyethyl)phosphine and Dithiothreitol for Use in Protein Biochemistry, Analytical Biochemistry) is maintained.

12. It is noted that Applicant addresses the patentability of claims 73-74 over Weischer et al. and Murphy in view of Laursen et al. further in view of Prugin despite the claims are newly added and not been examined in the prior action. The claims are new and subject to the grounds of rejections below. It is noted that the arguments are not persuasive as they are not commensurate in scope with the claims.

13. It is noted that Applicant's editorial comment is an opinion and bears no relevance to the details of the instant case.

New Grounds of Rejection

Due to the amendment with the addition of new claims the new grounds of rejection are applied:

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 69-70 and 72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

MPEP § 2163 states that, "[n]ew or amended claims which introduce elements or limitations which are not supported by the as-filed disclosure violate the written description requirement. Further, the MPEP states, "[w]hile there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure."

In the instant case, the added claims are drawn to a patient in need of nitroglycerin therapy consisting of unstable coronary syndromes, restenosis, heart failure, asthma, and rectal spasm with nitroglycerin and a dithiol and/or reductant selected from amifostine, thiobutyldiphenylphosphonium cation, dithiothreitol, dihydrolipoic acid, and tris (2-carboxyethylphosphine).

However, it is noted that there is appropriate support for dithiothreitol and dihydrolipoic acid as they are dithiols, and tris (2-carboxyethylphosphine) as a reductant for administration with nitroglycerin. There is no support for the administration of thiols with nitroglycerin for the method in the claims. Specifically, amifostine and thiobutyldiphenylphosphonium cation are thiols, not dithiols. Further, to classify them as such is not supported and would be repugnant to the art.

Further, as defined in the specification, there is a clear distinction stated between mitochondrial-selective thiols (amifostine-uncharged, thiobutyldiphenylphosphonium cation-charged), dithiols (dithiothreitol and dihydrolipoic acid), and other reductants (tris (2-carboxyethylphosphine). The specification addresses these compounds in different

groupings and the specification addresses the method for dithiols and/or reductants with the reductant being "other reductants" meaning not thiols or dithiols. There is no apparent support for this specific method to be applied with nitroglycerin and the thiols amifostine and thiobutyldiphenylphosphonium cation. The support for the thiols is to a different method directed to potentiating organic nitrates and transgenes.

There is no express, implicit, or inherent disclosure to support the thiols amifostine and thiobutyldiphenylphosphonium cation as instantly claimed.

There is also no support for dihydrolipoic acid to be termed as both a dithiol and/or a reductant, as the specification addresses it as a dithiol, not a reductant. The term "reductant" is used to address the compounds that are not thiols or dithiols such as tris (2-carboxyethylphosphine in the specification to distinguish the different groupings. The claims are to be given its broadest interpretation, but in light of the specification, there would be a distinction between thiols, dithiols, and reductants (which are other compounds not thiols or dithiols).

16. Claims 69-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of angina, an unstable coronary syndrome, it does not reasonably provide enablement for all coronary syndromes and conditions, restenosis, asthma, or rectal spasm. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Applicant has reasonably demonstrated that the specific dithiols: dithiothreitol (DTT), dihydrolipoic acid (DHLA) and tris (2-carboxyethylphosphine) are useful as a

therapeutic agent for delaying, postponing, and/or reducing nitroglycerin tolerance in angina.

However, the claims also encompass using the claimed compound to reverse nitroglycerin tolerance which is clearly beyond the scope of the instantly disclosed/claimed invention. Please note that the term "reverse" is an absolute definition which means to create a situation where the episode never happened, and, thus, requires a higher standard for enablement than does "therapeutic" or "treat", especially since it is notoriously well accepted in the medical art that the vast majority of afflictions/disorders suffered by mankind cannot be totally prevented or completely reversed with current therapies (other than certain vaccination regimes) – including preventing such disorders as myocardial infarcts, which is clearly not recognized in the medical art as being a totally preventable condition.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to all unstable coronary conditions, restenosis, asthma, and rectal spasms. Thus, the claims taken together with the specification imply the invention is capable of addressing each and every one of these conditions.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The state of the prior art shows that nitroglycerin is currently advised for use in angina but the benefits with or congestive heart failure have not been established to date, and are contraindicated in acute myocardial infarction, constrictive pericarditis, and pericardial tamponade (see Physician Desk Reference pages- submitted in prior action). As taught by Kennedy et al. (Airway response to sublingual nitroglycerin in acute asthma, JAMA), nitroglycerin was inadequate for the treatment of acute asthma and did not significantly change neither the forced expiratory volume nor the forced vital capacity of air for those tested showing that nitroglycerines in not adequate initial therapy for asthmatic attacks, in fact he teaches that its use could be dangerous. The unpredictability for the drug in the art is high and it is unclear what conditions nitroglycerin would be effective, much less what the outcomes would be when combined with another drug, resulting in an unclear expectation of what would be successful.

(5) The relative skill of those in the art:

The relative skill of those in the art is high.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance solely for angina in Examples XXXII and XXXIII.

However, the specification does not provide for all other unstable coronary condition, restenosis, asthma, and rectal spasms.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to the high degree of unpredictability in the art for nitroglycerin, it is unclear what conditions nitroglycerin would be effective, much less what the outcomes would be when combined with another drug. Without experimentation, as currently claimed, the scope of the invention would require undue experimentation of one skilled in the art to address each and every condition and every combination without a clear expectation of success.

As evidenced therein, along with the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Claims 69-72 are rejected.

17. Claims 73-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of angina, an unstable coronary syndrome, it does not reasonably provide enablement for the prevention of nitroglycerin tolerance. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Applicant has reasonably demonstrated dihydrolipoic acid (DHLA) is useful as a therapeutic agent for delaying, postponing, and/or reducing nitroglycerin tolerance in angina.

However, the claims also encompass using the claimed compound to prevent or reverse nitroglycerin tolerance which is clearly beyond the scope of the instantly disclosed/claimed invention. Please note that the term "prevent" is an absolute definition which means to stop from occurring or to create a situation where the episode never happened, and, thus, requires a higher standard for enablement than does "therapeutic" or "treat", especially since it is notoriously well accepted in the medical art that the vast majority of afflictions/disorders suffered by mankind cannot be totally prevented or completely reversed with current therapies (other than certain vaccination regimes) – including preventing such disorders as myocardial infarcts, which is clearly not recognized in the medical art as being a totally preventable condition.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to the prevention of nitroglycerine tolerance. Thus, the claims taken together with the specification imply the invention is able to have no nitroglycerin tolerance whatsoever.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The state of the prior art by Murphy teaches the concept that nitroglycerin appeared to relax arteries via two pathways. One required low concentration of nitroglycerin and a labile endogenous factor that was preserved by dithiothreitol but could be eliminated by ferricyanide, which would be the pathway affected in the invention addressed in the instant claims. However, there was a loss of effectiveness of CTT by the fourth protocol of the day, showing a reduction of effectiveness over time. There is a second pathway distinct pathway that required higher levels of nitroglycerin and the relaxation with DHAA significantly decreased the potency of nitroglycerin at the higher doses, which makes it less effective resulting in tolerance. Thereby the unpredictability of the art is very high and *prevention* of nitroglycerin tolerance is not feasible, only delaying, postponing, and/or reducing nitroglycerin tolerance is shown.

(5) The relative skill of those in the art:

The relative skill of those in the art is high.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for reduction of nitroglycerin tolerance for angina in Examples XXXII and XXXIII.

However, the specification does not provide prevention of nitroglycerin tolerance or for treatment of other conditions such asthma.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above; particularly with regards to the high degree of unpredictability in the art for nitroglycerin and the nitric oxide pathways, it is unclear what conditions absolute prevention of nitroglycerin tolerance would occur. Without experimentation, as currently claimed, the scope of the invention would require undue experimentation of one skilled in the art to accomplish this without a clear expectation of success.

As evidenced therein, along with the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Claims 73-74 are rejected.

18. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

19. Claims 69-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 69-70 recites the limitation "the patient is affected with a disorder" in claim 35. There is insufficient antecedent basis for this limitation in the claim.

20. Claims 71-72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 71-72 recites the limitation "the patient is affected with angina" in claim 35. There is insufficient antecedent basis for this limitation in the claim.

21. Claims 70 and 72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to where the dithiol and /or reductant is dihydrolipoic acid. This is confusing as the specification delineates dihydrolipoic acid to be a "dithiol" and does not refer to the compound as "reductant". The term "reductant" is utilized to address other compounds such as tris (2-carboxyethylphosphine that are not thiols or dithiols to distinguish the different groupings. The claims are attempting to classify the dihydrolipoic acid as both a "dithiol" and/or a reductant. It does not allow one of skill in the art to ascertain the metes and bounds of the invention.

For the purposes of prosecution, dihydrolipoic acid will be viewed as a dithiol.

Claim Rejections - 35 USC § 102

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. Claims 69- 74 are rejected under 35 U.S.C. 102(b) as being anticipated by Weischer et al. (DE 4420 102 A1).

Weischer et al. teaches the use of alpha-lipoic acid, also known as dihydrolipoic acid, in combination with cardiovascular drugs, including specific embodiments for nitroglycerin (glyceryl trinitrate).

It is noted that the translation previously provided is a machine translation from the European Patent Office and for clarity "alpha Liposaure" is alpha-lipoic acid and "Glyceroltrinitrate" is nitroglycerin.

Weischer teaches the combination of alpha-lipoic acid (enantiomers, derivatives or metabolites) and organic nitrates, including nitroglycerin in combination preparation. He teaches that the combination showed a greater anti-ischemic effect than when the nitroglycerin was administered alone. Thereby the combination of nitroglycerin and other nitrates with alpha-lipoic acid/dihydrolipoic acid (dithiol) showed a therapeutic anti-organic nitrate tolerance effect. As the patient population in need of nitroglycerin therapy would be the same patient population in need of reversal or postponement of nitroglycerin tolerance and the art would apply and the method of administering the compounds are the same and the resulting cascade is inherent.

There were in vitro and in vivo models performed.

The in vivo models were comprised of administering by balloon catheter to animals (dog and house pig) with follow up histological investigation. The combination is envisioned for angina pectoris among other conditions. Weischer teaches the composition and methods of administration for angina with humans (see DE 4420102,

Page 6, Table 1). Weischer goes on to claim the method of use in Claim 21 (citations are based on the translation provided – Specification: Page 1, paragraphs 1, 7, 9, 16-17 of 19 on page, Page 2, paragraphs 2-9 of 18 on page, Page 4, paragraph 2-10 of 28 on page, Page 6, paragraph 10-14 of 21 on page, Page 7, paragraph 14 of23 on page, Claim set: Page 2, claim 21).

All the critical elements are taught by the cited reference and thus the claims are anticipated.

Claim Rejections - 35 USC § 103

24. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

25. Claims 69 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy (Influence of redox compounds on nitrovasodilator-induced relaxations of rat coronary arteries, British Journal of Pharmacology) in view of Laursen et al. (In Vivo Nitrate Tolerance Is Not Associated With Reduced Bioconversion of Nitroglycerin to Nitric Oxide, Circulation).

Murphy teaches use of six redox compounds to test for their influence on nitrovasodilation.

The six redox compounds including dithiothreitol (DTT) - a dithiol reductant and ferricyanide - an anionic oxidant.

Murphy teaches that nitroglycerin has been used for decades and has remained a useful therapy against angina. Murphy also teaches the concept that the relaxation profiles suggested two pathways by which nitroglycerin-released nitric oxide. There was a loss in sensitivity to nitroglycerin over time (tolerance) in the control and in some of the redox compounds. However, DTT preserved the initial relaxation even through the fourth nitroglycerin protocol (resisted and delayed tolerance). Ferricyanide in contrast attenuated the initial relaxation during the first protocol. This taught that DTT preserves the process promoting nitric oxide release from nitroglycerin while the oxidant eliminated it. Murphy taught that tolerance would be by delayed with the use of a high-affinity, labile reductant or a low affinity reductant not glutathione.

Murphy does not expressly teach the administration of the dithiol and reductants to a patient.

Laursen et al. teaches the process of where in vitro data suggesting reduced bioconversion of nitroglycerin to nitric oxide contributed to nitroglycerin tolerance led to in vivo studies.

Laursen teaches that the next step after in vitro studies was to examine the in vivo validity of the hypothesis by measuring the nitroglycerin derived nitric oxide formation in a patient (rats). This was done with catherization of the rats. The study showed that tolerance is not associated with the in vivo bioconversion of the nitroglycerin to nitric oxide, but most likely from a substance derived form the endothelium (Abstract, Page 2, Introduction, Page 3, Methods- Animals section,

Induction of Nitrate Tolerance section, Page 5, Experimental Protocols section-study 1, Page 6, Study2-3, Page 10, Discussion section, Page 11-12)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to formulated an in vivo study after an in vitro study, as suggested by Laursen, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because it would be the natural progression for the development of any drug. There is lab testing, animal model testing and administration, human short-term clinical trials, long-term human clinical trials, and FDA approval, to reach mass manufacture for the market place.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

26. Claims 70 and 72-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy in view of Laursen et al. as applied to claims 35-38 and 40 above, and in view of Prugin et al. (Interplay between Vitamin E, Glutathione and Dihydrolipoic Acid in Protection against Lipid Peroxidation, Abstract only).

The teachings of Murphy in view of Laursen et al. are is discussed above especially the fact that Murphy taught that tolerance would be by delayed with the use of a high-affinity, labile reductant or a low affinity reductant that was not glutathione.

Murphy in view of Laursen et al. does not expressly teach the use dihydrolipoic acid.

Prugin et al. teaches that dihydrolipoic acid is an effective thiol, especially as a reducing agent. It was tested along with dithiothreitol (DTT) and glutathione in the presence of thiol-alkylating agents. DTT and dihydrolipoic acid were able to reverse the inhibition of the alkylating agents to various degrees. Glutathione however was not able to reverse the inhibitory effects. Reactivation of microsomal ATPase by the dihydrolipoic acid was mostly the reason for its protective effect on peroxidation making it an obvious choice for the incorporation in the teachings of Murphy in view of Laursen as a labile reductant that was not glutathione (see Abstract).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize dihydrolipoic acid, as suggested by Prugin, and produce the instant invention. As suggested by Murphy in view of Laursen, a high-affinity, labile reductant or a low affinity reductant that was not glutathione would be desirable to defer nitroglycerin tolerance.

Thereby, one of skill in the art would search for analogous or effective reductants in similar capacities to combine with the nitroglycerin. Prugin taught the dihydrolipoic acid is an effective thiol, especially as a reducing agent. One of skill in the art at the time

would utilize dihydrolipoic acid as it has many reductant and protective properties, especially in light of its ability to overcome inhibition in comparison to glutathione.

One of ordinary skill in the art would have been motivated to do this because dihydrolipoic acid is naturally found in the body so it as it would mostly likely not have negative side effects compared to other available reductants.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. It is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Conclusion

27. Claims 35-41 and 69-74 are rejected.

28. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GiGi Huang whose telephone number is (571) 272-9073. The examiner can normally be reached on Monday-Thursday 8:30AM-6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GH

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER